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the wrong amount, the fee for extension of time or any other fee that may be due in connection with this paper or with this application during its entire pendency may be charged to Deposit Account No. 08-1641. If a Petition for extension of time is needed, this paper is to be considered such Petition.

A Revocation of and a Power of Attorney reflecting a change in firm affiliation of the undersigned was mailed on July 21, 1998. The PTO records should be changed to reflect the new correspondence address for the undersigned, which is:

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Claims 1-90 are pending in the application. Claims 1-39 are amended. The amendments are designed to more particularly point out and distinctly claim the subject matter that applicant regards as the invention. Claims 40 -90 have been added. The amended claims and added claims find basis in the specification as originally filed.

The Examiner's attention is directed to copending U.S. application Serial No. 08/787,639 to Little et al., which was filed on the same day as this application.

Copies of two references cited and provided in connection with a previously submitted Information Disclosure Statement accompany this response.

INFORMATION DISCLOSURE STATEMENT

The Office Action mailed, March 19, 1998, contains copies of initialed PTOL-1449 forms mailed, as part of an Information Disclosure Statement, to the Patent Office on May 20, 1997 (date stamped in the Patent Office, May 23, 1997). All citations on the 1449 form, except reference AO, which cites an

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article by Kozal et al. (misspelled as Kozat) and reference AP, which cites an article by Wallace. Although it is believed that copies of these references were provided, for the Examiner's convenience, copies of reference AO and AP are attached. Applicant respectfully requests that the Examiner review reference AO and AP, make them of record in the file history of the application, and initial and date the PTOL form that is of record in the application.

REJECTION OF CLAIMS 2, 4, 5 AND 25-30 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 2, 4, 5 and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Various bases for this rejection are set forth and each is discussed in turn. Reconsideration of the grounds for rejection is respectfully requested in view of the amendments of the claims and the following remarks.

Relevant Law

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. The claim language is satisfactory if it reasonably "appraise[s] those skilled in the art" of the bounds of the claimed invention and is "as precise as the subject matter permits."

Shatterproof Glass Corp.v. Libby-Owens Ford Co, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir), cert dismissed, 106 S. Ct. 340 (1985).

1. Claim 2 is rejected because "a substrate" is allegedly confusing as to whether it is the same substrate recited in claim 1. Claim 27 allegedly has the same deficiency. It is respectfully submitted that the rejection of claim is obviated by amendment of the claims to recite "the substrate", thereby rendering the antecedent clear. Claim 27 does not recite this language.

2. Claim 4 is rejected because the "solvent of the matrix material" allegedly lacks antecedent basis. It is respectfully submitted that the rejection is

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obviated by amendment of the claim to recite that the solvent contains the matrix.

3. Claim 25 is rejected because "second location" in line 7 allegedly should be "first location." It is respectfully submitted that the rejection is obviated by amendment of the claim to recite "first location."

THE REJECTION OF CLAIMS 1-39 UNDER 35 U.S.C. § 103(a)

Claims 1-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deeg et al. (U.S. Patent No. 5,338,668) in view of Pfost et al. (U.S. Patent No. 5,108,703) because it is alleged that Deeg et al. teaches a method including the steps of providing a vesicle (number 3 in Figure 1) having an interior chamber containing a fluid, disposing the vesicle (number 3 in Figure 1) adjacent to a first location on the surface of a substrate (number 16 in Figure 1), controlling the vesicle to eject from the chamber a volume of the fluid to dispense the fluid at the first location of the surface of the substrate, and moving the substrate to a set of positions so that fluid is dispensed at each location of the set for forming an array of sample material. It is further alleged that the method described in Deeg et al. differs from the instantly claimed methods in that the substrate is moved to a set of positions, rather than moving the vesicle to each position. It is contended that a movable vesicle is conventional and Pfost et al., which allegedly teaches an automated analytical system including the step of moving a vesicle (number 54 in Figures 1 and 7) into a predetermined position adjacent to the surface of the substrate, evidences this.

It is concluded that it would have been obvious to have combined the method of Deeg et al. with the step of moving the vesicle as taught by Pfost et al. because the step of moving the vesicle as taught by Pfost et al. was conventional in the art.

The rejection is respectfully traversed insofar as it applies to any of claims 1-90.

The Claims

Claims 1 and its dependents, claims 22-24 and 87-90, are directed to methods for forming an array of a sample material on a surface of a substrate. The methods include the steps of providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing the sample material; without contacting the surface with the vesicle, disposing the vesicle adjacent to a first location on the surface of the substrate; providing mechanical pressure to the interior of the vesicle to eject from the chamber a nanoliter volume of the fluid to dispense the fluid at the first location of the surface of the substrate; and moving the vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a nanoliter volume of fluid is dispensed at each location of the set forming an array of sample material on the substrate.

Thus the method includes using mechanical pressure (i.e., not thermal pressure), such as by providing pressure with a pressure source or by deforming the chamber holding the fluid, and thereby dispensing a controlled volume (on the order of about nanoliter (i.e., less than 1 nanoliter to less than 100 nanoliters) of drop or spray onto a surface, but without touching the vesicle to the surface. Dependent claims specify the material that is deposited, the types of vesicle and means for applying pressure, and additional method steps.

Claims 25-30 are directed to methods for analyzing a material by providing a vesicle comprising a fluid containing the material in a solvent; and without contacting the surface with the vesicle dispensing controlled nanoliter volumes of the fluid on the substrate, and then analyzing the composition of the deposited material by mass spectrometry.

Claims 31-35 are directed to the systems for forming an array of a sample material on a surface of the substrate and for analyzing the array of sample material for chemical composition.

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Claims 36-39 are directed to the substrate having a surface carrying an array of a matrix material or matrix material and analyte for mass spectrometry analysis.

Claims 40-69 are directed to methods for dispensing nanoliter volumes of a material as an array onto the surface of a substrate using an assembly having a plurality of vesicles with interior chambers containing a fluid, arranged in the form of array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the material; using mechanical pressure, controlling each of the chambers to eject a nanoliter volume of the fluid from each vesicle onto the surface of the substrate aligned with the vesicles to form an array of deposited fluid on the substrate.

Claims 70-86 are directed to a method for dispensing nanoliter volumes of a material as an array on the surface of a substrate by providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom in which a nanoliter volume of fluid is loaded onto the end and onto the end of the vesicles of the pin assembly, and then dispensed by contacting the fluid, not the vesicle with the surface of the assembly.

The teachings of the cited references and differences from the claimed subject matter

Deeg et al.

Deeg et al. teaches a method for metered application of an analytical biochemical liquid from an bubble jet-type cartridge onto a target using heat to eject fluid. The bubble jet has a heating element held in contact with the liquid inside the jet. The heated liquid forms a vapor bubble inside the jet which increases air pressure, resulting in ejection of liquid.

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In one embodiment, the bubble jet is used to apply reagent in a two dimensional pattern on a fixed target (Figure 1). In a second embodiment, the jet is used to apply liquid onto a continuously moving target (Figure 2). Embodiments in which multiple jets held in a linear format are used for dispensing also are described.

Deeg et al. does not teach or suggest a method that uses mechanical pressure to dispense nanoliter volumes of material on a substrate. Deeg et al. only describes a bubble jet, which requires a heating element.

In addition, with respect to dependent claims, Deeg et al. also fails to teach or suggest steps for dispensing of analyte materials and matrix materials to the same location of the substrate for later analysis by a diagnostic tool such as a mass spectrometer. Furthermore, Deeg et al. fails to teach or suggest using a plurality of assemblies or narrow bore vesicles arranged in a matrix to dispense fluid in an array on a substrate. With respect to claims 31-35, Deeg et al. does not teach or systems for dispensing liquid

With respect to claims 36-39, Deeg et al. does not teach or suggest a substrate with an array of sample material suitable for mass spectrometry analysis, the array formed by a method comprising dispensing a matrix material mixed with a sample material by separately dispensing matrix material and analyte material to the same locations on the surface of a substrate. Deeg et al. also does not teach analysis of the material in the array on the surface by using a tool for compositional analysis such as a mass spectrometer.

With respect to the added claims, Deeg et al. does not teach a method using a pin tool in which drops of liquid on the end of each pin are contacted with the surface of the substrate without contacting the surface with the pin, nor does Deeg et al. teach or suggest an array of vesicles in which liquid is dispensed by mechanical pressure.

Pfost et al.

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Pfost et al. teaches an automated multi-purpose analytical chemistry processing center and workstation that has a movable table for supporting microtiter plates, a movable arm and a modular mobile pod for reciprocal movement along the arm. The workstation provides capabilities for automation of bioanalytical procedures that require reagent addition, other manual procedures and also provides for spectrophotometric measurements.

The instrument has a pod that can accept a variety of interchangeable modules, such as a fluid transport module for removal or addition of liquid reagent to a well, or module containing transducer means for measurement of physical characteristics of a sample. The liquid dispensing module is taught as a single tip or a linear array of tips (see figures 8 and 11b) for dispensing into standard 96 well type microtiter plates. Means for dispensing nanoliter quantities of fluid are not taught or suggested.

Pfost et al. also fails to teach or suggest dispensing a nanoliter volume of a fluid from a narrow bore vesicle or any vesicle by any means. In addition, Pfost et al. fails to teach or suggest steps for dispensing of analyte materials and matrix materials to the same location of the substrate for later analysis by a diagnostic tool such as a mass spectrometer. Furthermore, Pfost et al. fails to teach or suggest using a plurality of assemblies or narrow bore vesicles arranged in a matrix to dispense a plurality of fluid in an array on a substrate.

Pfost et al. does not teach or suggest a substrate with an array of sample material suitable for mass spectrometry analysis, the array formed by a method comprising dispensing a matrix material mixed with a sample material by separately dispensing matrix material and analyte material to the same locations on the surface of a substrate. Pfost et al. also does not teach analysis of the material in the array on the surface by using a tool for compositional analysis such as a mass spectrometer.

Thus, Pfost et al. fails to teach a method in which nanoliter volumes are dispensed using mechanical pressure.

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The Office Action fails to set forth a case of *prima facie* obviousness

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Analysis

It is respectfully submitted that the assertion that the method of Deeg et al. differs only from the instantly claimed methods in that the substrate is moved to a set of positions, rather than moving the vesicle to each position is inaccurate. As discussed above, there are numerous elements of significance which neither reference addresses. For example, neither reference in any combination teaches or suggests a method in which nanoliter volumes are

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dispensed using mechanical pressure, such as that produced by an external pressure source or by a transducer that deforms the interior space. Deeg et al. teaches a bubble jet printer in which a bubble is produced by heating. Pfof et al. teaches use of pipette tips, which are not designed to deliver volumes on the order of nanoliters.

Furthermore, Deeg et al. and Pfof et al. fail to teach or suggest using a plurality of assemblies or narrow bore vesicles arranged in a matrix to dispense a plurality of fluid in an array on a substrate.

With respect to claims 25 and its dependents and claims 26-39, the references also fail to teach or suggest a method comprising dispensing a matrix material or a combination of matrix and analyte material by applying a matrix and a sample material to the same locations on the surface of the substrate and compositional analysis of the material in the array (e.g., by mass spectrometry).

Thus, the references, singly or in any combination thereof, fail to teach or suggest several critical elements of the claimed subject matter. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

(1) There would have been no motivation to have modified the teachings of Deeg et al. with those of Pfof et al.

There is no suggestion in Deeg et al. to use any dispensing formats other than a heat element type inkjet printing device. Deeg et al. is directed to a bubble jet printing means. Pfof et al. teaches use of an elongated pipette tip, but provides no teachings to modify the bubble jet of Deeg et al. or associated apparatus to dispense a nanoliter volume of fluid.

Further, Deeg et al. arguably teaches away from methods that rely on mechanical pressure by describing the deficiencies in the teachings of prior art jets using mechanical deformation. Deeg et al. provides a solution to such problems by providing methods that use bubble jet dispensing means. There would have been no motivation to have modified the bubble jet of Deeg et al., since that is the thrust of the patent.

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(2) The combination of teachings of the cited references does not result in the instantly claims methods, substrates or systems

Furthermore, the combination of teachings of Deeg et al. with those of Pfof et al. do not result in the instantly claimed methods, substrates or systems. As noted, neither reference teaches or suggests means for or a method for dispensing nanoliter volumes using mechanical pressure. None of the references teaches or suggests a method of analysis of materials deposited in nanoliter volumes, and none mentions mass spectrometric analyses or substrates with arrays of materials for mass spectrometric analysis, or systems for such analyses.

Furthermore, none of the references mentions a method using a pintool to dispense nanoliter volumes of material on a substrate.

Thus, the combination of teachings of the cited references is deficient in critical elements of the claimed subject, including the dispensing method, resulting substrates and the systems. Therefore, the combination of teachings of the references does not result in the claimed methods, substrates or systems.

(3) The Rejection over Deeg et al. in view of Pfof et al. is Based on Improper Use of Hindsight.

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

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In this instance, it appears that the Examiner has combined the teachings of the prior art with those of the instant application in order to produce the instantly claimed methods, substrates and systems. It is only through hindsight analysis that one can imbue the prior art with the various elements of the claimed subject matter.

As discussed above, there are numerous deficiencies in the teachings of the cited art. Nothing in the prior art teaches or suggests a system for dispensing nanoliter volumes of a material as an array on the specified substrates for further analysis, nor methods for dispensing nanoliter volumes using methods other than thermal pressure.

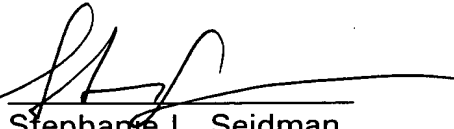
Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: LITTLE et al.

Serial No.: 08/786,988

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For: SYSTEMS AND METHODS FOR PREPARING
AND ANALYZING LOW VOLUME ANALYTE
ARRAY ELEMENTS

Art Unit: 1743

Examiner: Le, L.



ATTACHMENTS TO AMENDMENT

1. Kozal et al. (1996) Nature Medicine 2:753-759; and
2. Wallace (1997) Laboratory Automation News 1:6-9.

Attorney Docket No. 24736-2001D

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